REMARKS

In the Office Action dated March 22, 2005, the Examiner maintained the rejection of claims 1-10 and 23-29 as being non-enabled under 35 USC 112, first paragraph.

The rejection is based in large part on applicant's use of the functional language "therapeutic agent", which is used in claims 1 and 23 to describe the gene that is encapsulated within the liposome. Applicant amends claims 1 and 23 to remove the objected to functional language. In place of the functional language, applicant defines the gene as being selected from the specific genes as originally claimed in claim 3. Claim 3 has been canceled as now being a duplicate of claim 1 and claim 5 is also canceled as being broader than claim 1, as now amended.

The claims, as now amended, no longer inlcude a functional element that requires a therapeutic effect. Accordingly, applicant respectfully requests that the rejection based on non-enablement under 35 USC 112, first paragraph be reconsidered and withdrawn.

It also should be noted that applicant respectfully disagrees with the Examiner's position that the expression of ß-galactosidase cannot easily be extended to a "therapeutic agent". (See page 6 of Office Action beginning at line 3).

The present application provides evidence for delivery of the ß-galactosidase gene to the eye of the mouse and the primate (Rhesus monkey). The ß-galactosidase gene is generally regarded as a 'reporter' gene, as pointed out by the Examiner. However, the ß-galactosidase gene is also a therapeutic gene. Humans express a ß-galactosidase gene, and a mutation in the ß-galactosidase gene causes 2 different lysosomal storage disorders, Morquio disease type B (mucopolysaccharidosis type IV-B), or GM1-gangliosidosis, a sphingolipidosis. The Genbank accession number for the human ß-galactosidase gene is NP_000395. Serious ocular manifestations are associated with both Morquio disease type B and GM1-gangliosidosis.

The present application shows the successful delivery of the ß-galactosidase gene to the eye, and the associated functional outcome of this delivery, i.e., the positive histochemical reaction of the ß-galactosidase histochemistry shows that functional ß-galactosidase enzyme

has been delivered to the eye with the requisite enzymatic activity associated with the functional expression of this gene. Moreover, the application shows high level of luciferase gene expression in the monkey retina, and this level of luciferase gene expression in the monkey eye is 50-fold higher than the level of luciferase gene expression in the mouse or rat brain (1, 2). The luciferase gene was delivered to mouse or rat brain with the same receptor-specific liposome delivery system as used to show therapeutic effects in experimental brain cancer in the mouse with an epidermal growth factor receptor antisense gene (3), or experimental Parkinsons disease in the rat with a tyrosine hydroxylase gene (4).

The Examiner cites a review by Verma on viral gene therapy, which discusses the inability to maintain a therapeutic level of expression with cationic liposomes. However, Verma was only aware of cationic liposomes, but was not aware of the receptor specific liposomes comprising the present invention. Because the terms, 'cationic liposomes' cited by Verma, and the 'receptor-specific liposomes' described in the present application share the common term, 'liposome,' the Examiner assumes these are comparable formulations and compositions. In fact, these are not comparable formulations, as shown in the Table submitted in applicant's Amendment dated December 21, 2004. The Examiner focuses on charge (anionic vs. cationic), but this is only 1 of several distinguishing features between the formulation described by Verma and the present formulation of receptor-specific liposomes (see first Table of the 12/21/04 Amendment).

Verma teaches viral gene therapy, which permanently alters the host genome, and causes serious problems associated with insertional mutagenesis. In contrast, the present application enables a reversible form of gene therapy, owing to the episomal nature of gene expression with receptor-specific liposomes. The Examiner argues that the reversible nature of episomal gene expression "does not address how the therapeutic nature of the agent is maintained in the absence of its expression." The claims, as presently amended, do not require that the therapeutic effect shall outlast the expression of the gene. Moreover, there is no dictum that says gene medicines, or gene therapy, must be permanent. Episomal-based gene medicines are given at repeat intervals, just like any other medicine. The periodicity of repeated

administration of the gene medicine is a function of the persistence of expression of the plasmid-based gene medicine in vivo.

The receptor-specific liposome as set forth in the present application does, in fact, deliver a therapeutic agent, as the ß-galactosidase gene is missing in lysosomal storage disorders discussed above. The present invention goes beyond the gene therapy taught by Verma, in that the present invention involves a new approach to gene delivery, which allows therapeutic levels of a exogenous gene in the eye without the use of viral vectors, and with a simple intravenous administration of the formulation. In contrast, the viral gene therapy, or the non-viral gene therapy (e.g. cationic liposomes), taught by Verma, require direct injection into the eye. Direct injection into the eye was required, because none of the gene delivery approaches reviewed by Verma could access the eye following intravenous administration. In contrast, the use of receptor-specific liposomes in accordance with the present invention allows the claimed gene to access the eye from the blood following an intravenous administration.

References (copies attached):

(1) Zhang, Y., Schlachetzki, F., Li, J.Y., Boado, R.J., and Pardridge, W.M. (2003): Organ-specific gene expression in the Rhesus monkey eye following intravenous non-viral gene transfer. Mol. Vis., 9: 465-472.

(2) Zhang, Y., Schlachetzki, F., and Pardridge, W.M. (2003): Global non-viral gene transfer to the primate brain following intravenous administration. Mol. Ther., 7: 11-18.

(3) Zhang, Y., Zhu, C., and Pardridge, W.M. (2002): Antisense gene therapy of brain cancer with an artificial virus gene delivery system. Mol. Ther., 6: 67-72.

(4) Zhang, Y., Calon, F., Zhu, C., Boado, R.J., and Pardridge, W.M. (2003): Intravenous non-viral gene therapy causes normalization of striatal tyrosine hydroxylase and reversal of motor impairment in experimental Parkinsonism. Human Gene Therapy, 14: 1-12.

In view of the above amendments and remarks, applicant respectfully requests that this application be reconsidered and allowed. The amendments to the claims do not raise any new issues that would require a further search. Instead, the amendments place the claims in a better condition for allowance. Accordingly, the amendments are appropriately made after Final Rejection.

Respectfully Submitted,

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/David J. Oldenkamp/
David J. Oldenkamp, Reg. # 29,421
SHAPIRO & DUPONT LLP
233 Wilshire Boulevard, Suite 700
Santa Monica, California 90401
(310) 319-5411 (Telephone)
(310) 319-5401 (Facsimile)